

## **Development of a Physiologically Based Pharmacokinetic and Pharmacodynamic (PBPK/PD) Model to Quantitate Biomarkers of Exposure to Organophosphorus Insecticides**

**Authors:** Charles Timchalk, Ahmed A. Kousba and Torka S. Poet  
Battelle, Pacific Northwest Division, Richland, WA

This project entails development and validation of a PBPK/PD model for the organophosphorus insecticide chlorpyrifos to quantitate biomarkers of dosimetry and cholinesterase (ChE) inhibition in young rats and children. It is hypothesized that an age-dependent decrement in chlorpyrifos metabolism correlates with the increased sensitivity of young animals, and potentially children, to organophosphate insecticides. The experimental approach involved developing algorithms to calculate age-dependent physiological and metabolic parameters and applying them to a PBPK/PD model to adequately describe the blood and tissue time-course of chlorpyrifos, and the metabolites chlorpyrifos-oxon and trichloropyridinol. Once fully developed, the model will be utilized to quantitate biomarkers of exposure and response (ChE inhibition) during neonatal/juvenile development (young rats and children). Coupled with model development, relevant *in vivo* and *in vitro* experiments needed to refine model parameters, validate model response and to assess the feasibility of utilizing saliva as a biomonitoring matrix for dosimetry and esterase inhibition have been conducted. Studies have focused on the development of analytical methods, acquisition of *in vivo* and *in vitro* data and the further refinement of the PBPK/PD model. Initial analytical methods were developed for the quantitation of chlorpyrifos and major metabolites. These methods have been used to support both *in vitro* and *in vivo* experiments. *In vitro* studies were conducted to evaluate the role that intestinal and hepatic metabolism may play in both the activation and detoxification of chlorpyrifos and the parameter estimates obtained from these studies are being used to further refine the PBPK/PD model. Likewise, to evaluate the potential utility of saliva for biomonitoring, studies were undertaken to characterize the total salivary ChE activity and estimate the kinetic parameters of *in vitro* and *in vivo* interaction of chlorpyrifos-oxon with rat salivary ChE. These results suggest that saliva may be a useful biological matrix for monitoring chlorpyrifos exposure and response, either through measuring the metabolite levels or the degree of ChE inhibition. These data have been used for further validation of the PBPK/PD model for chlorpyrifos. The PBPK/PD model has been modified to allometrically scale (based on body weight) the age-dependent development of metabolism enzymes and ChE enzyme activity and simulations were compared against available data. The model suggests that even though neonatal rats have lower metabolic capacity, it is adequate to detoxify chlorpyrifos at relevant environmental exposure levels. These simulations are consistent with differences in the acute toxicity response noted between neonatal and adult rats. To assess the impact of variability associated with the human chlorpyrifos-oxonase (PON1) polymorphisms in adults on the theoretical concentration of chlorpyrifos-oxon in the human brain, a Monte Carlo analysis was conducted. The results suggested that the PON1 polymorphism had the greatest impact on target tissue dosimetry at dose levels that overwhelmed other detoxification pathways.